Genetic Epidemiology 20:34–43 (2001)

A Weighted Test Using Both Extreme Discordant and Concordant Sib Pairs for Detecting Linkage

Zhaohai Li[1]* and Joseph L. Gastwirth[2,3]

[1]*The Biostatistics Center, Department of Statistics, George Washington University, Rockville, Maryland*
[2]*Department of Statistics, George Washington University, Washington, DC*
[3]*Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, Maryland*

Statistical procedures using extremely discordant and concordant sib-pairs have been developed for mapping quantitative trait loci in humans. To improve the power of the existing methods, test statistics placing greater weight on the more discordant or more concordant pairs are proposed. Because the optimum choice of weights would depend on the underlying genetic model, which is not usually known, a test with simple weights is suggested. This test is shown to have greater power than the currently available ones for a variety of genetic models. Genet. Epidemiol. 20:34–43, 2001. © 2001 Wiley-Liss, Inc.

Key words: linkage analysis; quantitative trait locus; weighted tests

INTRODUCTION

Recent developments in molecular genetics have expanded opportunities to study the genetic origin of complex diseases. Genetic analysis of quantitative trait loci (QTLs) aids in understanding the genetic basis of complex traits. Sib-pair designs are an important tool for investigating QTLs in humans [Haseman and Elston, 1972; Fulker and Cardon, 1994; Kruglyak and Lander, 1995; Sham et al., 1997]. Sib pairs are relatively easy to ascertain and their environments usually are similar. The methods used to analyze sib-pair data can be parametric or non-parametric.

Contract grant sponsor: National Cancer Institute; Contract grant number: CA64363; Contract grant sponsor: National Science Foundation.

*Correspondence to: Zhaohai Li, Ph.D., The Biostatistics Center, George Washington University, 6110 Executive Blvd., Suite 750, Rockville, MD 20852. E-mail: zli@biostat.bsc.gwu.edu

Received for publication 24 November 1999; revision accepted 12 January 2000

Non-parametric methods of linkage analysis are largely based on allele sharing. The measure of allele sharing is the number of alleles that are identical by descent (IBD) in both members of the pair. Roughly speaking, sib pairs with similar phenotypes should have more alleles IBD at the marker locus when the marker and trait loci are close to each other than two sibs with dissimilar phenotypes. Under certain assumptions, Haseman and Elston [1972] showed that the expected squared difference of the quantitative trait values between two sibs is a linear function of the proportion of alleles shared IBD at the test marker locus with a negative slope. The slope is a function of the recombination fraction between the trait and marker loci. This linear regression relationship has been widely used in sib-pair linkage analysis of quantitative traits. Several related methods that select sib-pairs based on their trait values have greater power than the original test [Blackwelder and Elston, 1982; Carey and Williamson, 1991; Eaves and Meyer, 1994; Risch and Zhang, 1995].

Three types of sib pairs selected on the basis of trait values provide most power to detect linkage for a QTL: extremely discordant (ED) sib-pairs in which one has a high and the other a low trait value and extremely concordant (EC) for high or low trait values [Risch and Zhang, 1995, 1996; Zhang and Risch, 1996; Zhao et al., 1997]. They investigated the power of three sib-pair designs under different genetic models and concluded that the ED sib-pair design has the greatest power. Hence their recommendation is that the ED sib-pair design is the choice for linkage study of QTLs in humans. Eaves and Meyer [1994] first introduced the notion of extreme sib-pairs and also obtained the power of ED sib-pairs by simulation.

The existing procedures give each ED (EC) pair the same weight. Rao [1998] found that these methods can be improved by exploiting the quantitative variability in the tails of the distribution of a trait. This paper develops a test giving greater weight to the more discordant (concordant) ED (EC) pairs. The idea is motivated by the classical two-sample normal scores rank test [Randles and Wolfe, 1979], which gives greater weight to the extreme ranks in the combined sample. It is shown that when the trait distribution is normal, these weighted tests have more power than the currently used procedures.

WEIGHTED TESTS

Let y_{1i} and y_{2i} denote the trait values for two sibs in a sib-pair study. We assume that the trait values have the following structure:

$$y_{1i} = \mu + g_{1i} + \mathrm{e}_{1i}$$
$$y_{2i} = \mu + g_{2i} + \mathrm{e}_{2i}$$

where μ is the overall mean, g_{1i} and g_{2i} represent genetic contributions to the trait values, and e_{1i} and e_{2i} are residuals.

We consider a single locus with two alleles A_1 and A_2. The allele frequencies of A_1 and A_2 are p and $q = 1 - p$, respectively. The mean trait values of individuals with three genotypes are defined as follows:

A_2A_2	A_2A_1	A_1A_1
–a	d	a

Then, the additive genetic variance is $\sigma_A^2 = 2pq[a + (q - p)d]^2$ and the dominance variance is $\sigma_D^2 = (2pqd)^2$. The total genetic variance is the sum of the additive and dominance variances, that is, $\sigma_G^2 = \sigma_A^2 + \sigma_D^2$. Let σ_E^2 be the residual variance for each genotype and ρ be the residual correlation coefficient between two sibs. The heritability owing to the trait locus is $\sigma_G^2/(\sigma_G^2 + \sigma_E^2)$. For simplicity, we assume that $\sigma_E^2 = 1$.

Recall the mean shared IBD statistic used by Risch and Zhang [1995] for ED sibpairs. Let Y_i denote the number of shared IBD for a given ED sib pair. Then, under the null hypothesis H_0 (no linkage), Y_i has the following distribution:

$Y_i =$	2	1	0
Probability	¼	½	¼

Define

$$n_0 = \sum_{i=1}^{N} I_{\{Y_i=0\}}, \quad n_1 = \sum_{i=1}^{N} I_{\{Y_i=1\}}, \quad n_2 = \sum_{i=1}^{N} I_{\{Y_i=2\}},$$

where N is the number of ED sib pairs selected for genotyping and $I_{\{Y_i=0\}}$ is an indicator function, which is one if the ith sib pair has zero IBD allele and zero otherwise, the indicators $I_{\{Y_i=1\}}$ and $I_{\{Y_i=2\}}$ are defined similarly. With these notations, n_k is the number of extreme discordant sibpairs who have k shared IBD, $k = 0, 1, 2$. The mean test statistic is the proportion of shared IBDs among the N selected sib pairs, i.e.,

$$\frac{1}{2N}(2n_2 + n_1) = \frac{1}{N}(n_2 + \frac{1}{2}n_1) = \frac{1}{2N}[N - (n_0 - n_2)].$$

This test statistic is similar to the mean test of the affected sib-pair (ASP) design [Blackwelder and Elston, 1985] and is equivalent to

$$T_{ED} = (n_0 - n_2) = \sum_{i=1}^{N} (I_{\{Y_i=0\}} - I_{\{Y_i=2\}}) \tag{1}$$

Under H_0 (no linkage), (n_0, n_1, n_2) has a trinomial distribution with parameters (¼, ½, ¼). It follows that

$$E_{H_0}(T_{ED}) = 0, \qquad Var_{H_0}(T_{ED}) = \frac{N}{2}.$$

Under the alternative hypothesis H_1, there is linkage between the trait and marker loci, and therefore (n_0, n_1, n_2) has a trinomial distribution with parameters $(p_0^{ED}, p_1^{ED}, p_2^{ED})$, where $p_0^{ED} = P\{Y_i = 0|ED\}$, $p_1^{ED} = P\{Y_i = 1|ED\}$, and $p_2^{ED} = P\{Y_i = 2|ED\}$. Notice that $p_0^{ED} \approx$ ¼ and $p_2^{ED} \ll$ ¼ because the pairs are discordant. Therefore,

$$E_{H_1}(T_{ED}) = N(p_0^{ED} - p_2^{ED}) = N\tau^{ED},$$

$$Var_{H_1}(T_{ED}) = N[p_0^{ED} + p_2^{ED} - (p_0^{ED} - p_2^{ED})^2] = N\nu^{ED}$$

where $\tau^{ED} = p_0^{ED} - p_2^{ED}$, and $\nu^{ED} = [p_0^{ED} + p_2^{ED} - (p_0^{ED} - p_2^{ED})^2]$.

The test statistic in equation (1) has an asymptotically normal distribution under both H_0 and H_1. In terms of the parameters p_0^{ED}, p_2^{ED}, H_0 may be re-stated as

$$p_0^{ED} - p_2^{ED} = 0,$$

and H_1 as

$$p_0^{ED} - p_2^{ED} > 0.$$

Thus, we reject H_0 if T_{ED} is large. The power formula for T_{ED} is given by

$$1 - \beta = 1 - \Phi\left(\frac{z_{1-\alpha}\sqrt{\frac{N}{2}} - N\tau^{ED}}{\sqrt{N\nu^{ED}}} \right) \tag{2}$$

where α and $1 - \beta$ are the desired significance level and power, $z_{1-\alpha}$ is the $(1 - \alpha)$th percentile point of the standard normal distribution, and Φ is the standard normal distribution function. Solving equation (2), we obtained the sample size formula

$$N = \frac{(z_{1-\alpha} - z_\beta\sqrt{2\nu^{ED}})^2}{2(\tau^{ED})^2}. \tag{3}$$

Notice the ν^{ED} is a decreasing function of τ^{ED}. Since $z_{1-\alpha} > 0$ and $z_\beta < 0$, the sample size N decreases as τ^{ED} increases, i.e., the larger τ^{ED} is, the more power the test has. Hence, τ^{ED}, the difference between the probabilities of having no allele shared IBD and of sharing two alleles IBD, is a key parameter determining the power of the ED sib-pair design.

The new procedure is motivated by the realization that sib pairs with one member in the upper 5% of the trait distribution and the other in the lowest 5% are more discordant than sib pairs in the upper and lower 10%. Thus, they are more informative than the other ED pairs and should receive more weight. Generalized weighted test statistics are defined by ordering the ED pairs by the difference in their trait values. Thus, ED_1 is the pair with the smallest difference between the trait values and ED_N is the pair with the largest difference. The weighted statistic is

$$T_{ED}^{w} = \sum_{i=1}^{N} w_i (I_{\{Y_{i=0}\}} - I_{\{Y_{i=2}\}}), \tag{4}$$

where

$$w_i = \frac{p_0^{ED_i} - p_2^{ED_i}}{\sum_{i=1}^{N}(p_0^{ED_i} - p_2^{ED_i})},$$

$$p_0^{ED_i} = P\{Y_i = 0 \mid ED_i\}, \qquad p_2^{ED_i} = P\{Y_i = 2 \mid ED_i\}.$$

The parameters $p_0^{ED_i} = P\{Y_i = 0|ED_i\}$ and $p_2^{ED_i} = P\{Y_i = 2|ED_i\}$ are functions of trait values of the given sib pair. Procedures for computing $p_2^{EDi} = P\{Y_i = 2|ED_i\}$ can be obtained from Risch and Zhang [1995, 1996].

Under H_0,

$$E_{H_0}(T_{ED}^w) = 0, \qquad Var_{H_0}(T_{ED}^w) = \frac{1}{2}\sum_{i=1}^{N} w_i^2.$$

Under H_1

$$E_{H_1}(T_{ED}^w) = \mu = \sum_{i=1}^{N} w_i \tau^{ED_i}, \quad Var_{H_1}(T_{ED}^w) = \sum_{i=1}^{N} w_i \nu^{ED_i},$$

where $\tau^{ED_i} = p_0^{ED_i} - p_2^{EDi}$ and $\nu^{ED_i} = p_0^{ED_i} + p_2^{EDi} - (p_0^{ED_i} - p_2^{EDi})^2$. As usual, the mean and variance are conditional on the trait values.

The test for linkage is

$$H_0 : \mu = 0, \quad \text{versus} \quad \mu > 0.$$

We reject H_0 and declare linnkage when T_{ED}^w is large. The power formula for detecting linkage by using the test statistic T_{ED}^w in equation (4) is

$$1 - \Phi\left(\frac{z_{1-\alpha}\sqrt{\frac{1}{2}\Sigma_{i=1}^{N} w_i^2} - \Sigma_{i=1}^{N} w_i \tau^{ED_i}}{\sqrt{\Sigma_{i=1}^{N} w_i^2 \nu^{ED_i}}} \right). \tag{5}$$

We now consider the extremely concordant sib-pair design. The test statistic of Risch and Zhang for detecting linkage based on EC sib pairs is equivalent to

$$T_{EC} = n_2 - n_0 = \sum_{i=1}^{N} (I_{\{Y_{i=2}\}} - I_{\{Y_{i=0}\}}). \tag{6}$$

Analogous to equation (4), a weighted test statistic based on EC sib pairs can be defined.

The power of the EC and ED designs depends on the difference between the conditional probabilities of having 0 and 2 alleles shared IBD. The only change is the sign of the difference between these probabilities. Having no alleles shared IBD is more likely for ED pairs and less likely for EC pairs.

Gu et al. [1996] proposed a test combining the ED and EC pairs. Li and Zhang [2000] proposed a similar test incorporating both extremely discordant and concordant pairs into one test. These methods gave equal weight to all ED or EC pairs. Here, we propose the following weighted test statistic

$$T_C^w = \sum_{i \in ED} w_i (I_{\{Y_{i=0}\}} - I_{\{Y_{i=2}\}}) + \sum_{i \in EC} w_i (I_{\{Y_{i=2}\}} - I_{\{Y_{i=0}\}}), \tag{7}$$

where for $i \in ED$

$$w_i = \frac{p_0^{ED_i} - p_2^{ED_i}}{\Sigma_{i=1}^{N}(p_0^{ED_i} - p_2^{ED_i}) + \Sigma_{i=1}^{N}(p_2^{EC_i} - p_0^{EC_i})},$$

where for $i \in EC$

$$w_i = \frac{p_2^{EC_i} - p_0^{EC_i}}{\Sigma_{i=1}^{N}(p_2^{EC_i} - p_0^{EC_i}) + \Sigma_{i=1}^{N}(p_0^{ED_i} - p_2^{ED_i})}.$$

Let

$$\mu = \sum_{i \in ED} w_i(p_0^{ED_i} - p_2^{ED_i}) + \sum_{i \in EC} w_i(p_2^{EC_i} - p_0^{EC_i}).$$

Then, test for linkage by using the statistics T_C^w in equation (7) is equivalent to

$$H_0 : \mu = 0 \quad \text{versus } H_1 : \quad \mu > 0$$

Reject H_0 when T_C^w is large. The power formula for detecting linkage with the combined weighted test is

$$1 - \Phi\left(\frac{z_{1-\alpha}\sqrt{\frac{1}{2}[\Sigma_{i\in ED} w_i^2 + \Sigma_{i\in EC} w_i^2]} - [\Sigma_{i\in ED} w_i \tau^{ED_i} + \Sigma_{i\in EC} w_i \tau^{EC_i}]}{\sqrt{\Sigma_{i\in ED} w_i^2 v^{ED_i} + \Sigma_{i\in EC} w_i^2 v^{EC_i}}} \right).$$

SAMPLE SIZE

To illustrate that the weighted tests often have more power than non-weighted ones, we consider the following situation: suppose N ED sib pairs are selected for genotyping in a linkage study based on their trait values with one sib in the top 10% of the distribution and the other in the bottom 10% (T1B1). The corresponding parameters are p_0^{ED} and p_2^{ED} for T1B1 sib pairs. Now further sub-divide the top 10% of the trait value into two intervals at the upper 5% point and the bottom 10% into two intervals at the lower 5% point. The N T1B1 sib pairs fall into four groups: 1) one sib is between the 90th and 95th percentile and the other is between the 5th and 10th percentile; 2) one is between the 90th and 95th percentile and the other is in the bottom 5%; 3) one is in the top 5% and the other is between the 5th and 10th percentile; 4) one is in the top 5% and the other is in the bottom 5%. The corresponding parameters for the four groups are denoted by p_0^{EDi}, p_2^{EDi} i = 1, 2, 3, 4, and the observed numbers of sib pairs with 0 and 2 alleles shared IBD for the four groups are n_0^i, n_2^i, i = 1, 2, 3, 4. The weighted test statistic for detecting linkage is defined by

$$T_{ED}^w = \sum_{i=1}^{4} w_i(n_0^i - n_2^i), \tag{8}$$

where

$$w_i = \frac{p_0^{ED_i} - p_2^{ED_i}}{\Sigma_{i=1}^4 (p_0^{ED_i} - p_2^{ED_i})}.$$

The sample size formula for the weighted test is given by

$$N = \frac{(z_{1-\alpha}\sqrt{a} - z_\beta \sqrt{d})^2}{b^2} \tag{9}$$

where

$$a = \frac{1}{2}\sum_{i=1}^4 w_i^2 r_i, \quad d = \sum_{i=1}^4 w_i^2 r_i v^{ED_i}, \quad b = \sum_{i=1}^4 w_i r_i \tau^{ED_i},$$

$$\tau^{ED_i} = p_0^{ED_i} - p_2^{ED_i}, \; v^{ED_i} = p_0^{ED_i} + p_2^{ED_i} - (p_0^{ED_i} - p_2^{ED_i})^2,$$

$r_i = N_i/N$, N_i is the number of sib pairs in each of the four groups, and $N_1 + N_2 + N_3 + N_4 = N$.

Similarly one can order the differences in trait values of the EC pairs and divide them into four groups. The statistic is

$$T_{EC}^w = \sum_{i=1}^4 w_i (n_2^i - n_0^i), \tag{10}$$

where

$$w_i = \frac{p_2^{EC_i} - p_0^{EC_i}}{\Sigma_{i=1}^4 (p_2^{EC_i} - p_0^{EC_i})}.$$

The sample size needed to achieve power $1 - \beta$ using the test statistic in (10) is

$$N = \frac{(z_{1-\alpha}\sqrt{e} - z_\beta \sqrt{f})^2}{g^2} \tag{11}$$

where

$$e = \frac{1}{2}\sum_{i=1}^4 w_i^2 r_{i,} \qquad f = \sum_{i=1}^4 w_i^2 r_i v^{EC_i}, \qquad g = \sum_{i=1}^4 w_i r_i \tau^{EC_i},$$

$$\tau^{EC_i} = p_2^{EC_i} - p_0^{EC_i}, \quad v^{EC_i} = p_0^{EC_i} + p_2^{EC_i} - (p_0^{EC_i} - p_2^{EC_i})^2,$$

$r_i = N_i/N$, N_i is the number of sib pairs in each of the four groups, and $N_1 + N_2 + N_3 + N_4 = N$.

The sample sizes needed by the tests T_{ED} in (1) and T_{ED}^w in equation (8) using only ED pairs are assessed by equations (3) and (9) with $r_i = 0.25$, $i = 1, 2, 3, 4$. The prameters p_0^{ED}, p_2^{ED}, p_0^{EDi}, p_2^{EDi} depend on the trait distribution and genetic parameters, such as gene frequency, heritability, and dominance relationships. The numeri-

TABLE I. Required Number of ED Sib Pairs to Detect Linkage for an Additive Model $\alpha = 0.0001$ and $1 - \beta = 0.8$

	H ($\rho = 0$)				H ($\rho = 0.4$)			
P	0.05	0.1	0.2	0.3	0.05	0.1	0.2	0.3
0.1	4,716[a]	1,117	251	105	882	221	65	39
	(6,827)[b]	(1,647)	(378)	(155)	(1,367)	(342)	(94)	(52)
0.3	4,551	1,048	225	88	933	236	63	31
	(6,449)	(1,482)	(314)	(120)	(1,394)	(346)	(88)	(42)
0.5	4,532	1,040	222	86	940	238	63	30
	(6,405)	(1,464)	(308)	(116)	(1,397)	(347)	(87)	(40)

[a]Sample size based on equation (9) for weighted test.
[b]Sample size based on equation (3) for unweighted test.
H, heritability; ρ, residual correlation coefficient; *P*, allele frequency.

cal results given in Table I show that the new test requires smaller sample sizes to achieve the same power as the standard test for the additive model. Similar results were obtained for the recessive and dominant models and can be obtained from the authors (Z.L.).

Sample-size comparions between T_{EC} in equation (6) and T_{EC}^{w} in equation (10) for concordant pairs are made according to the formulas in Risch and Zhang [1995] and equation (11) with $r_i = 0.25$, $i = 1, 2, 3, 4$. The numerical results presented in Table II indicate that the weighted test is more powerful for the additive model. Similar numerical results were obtained for the recessive and dominant models. Table III presents sample sizes needed for the weighted and unweighted [Li and Zhang, 2000] tests using both ED and EC pairs. The table is based on an equal mixture of ED and EC pairs and equal fractions ($r_i = 0.25$) of each category of ED or EC pairs. The results indicate a substantial gain in power for the new procedure.

DISCUSSION

Under the assumption that there is no recombination between trait and marker loci and sib pairs are fully informative, we derived a weighted test for ED and EC sib-pair designs. The weighted test is more powerful than the previously proposed unweighted tests. The numerical results in Tables I and II show that the sample sizes

TABLE II. Required Number of EC Sib Pairs to Detect Linkage for an Additive Model $\alpha = 0.0001$ and $1 - \beta = 0.8$

	H ($\rho = 0$)				H ($\rho = 0.4$)			
P	0.05	0.1	0.2	0.3	0.05	0.1	0.2	0.3
0.1	2,067[a]	501	165	106	5,860	1,233	291	145
	(3,281)[b]	(778)	(235)	(140)	(8,650)	(1,842)	(419)	(194)
0.3	4,045	1,060	314	166	9,776	2,328	574	263
	(5,817)	(1,497)	(428)	(221)	(13,289)	(3,147)	(761)	(342)
0.5	5,818	1,676	531	286	12,873	3,362	910	433
	(7,967)	(2,232)	(676)	(351)	(16,843)	(4,326)	(1,136)	(526)

[a]Sample size based on equation (11) for weighted test.
[b]Sample size based on formula in Risch and Zhang [1995] for unweighted test.

TABLE III. Required Number of Sib Pairs to Detect Linkage for ED and EC Sib Pairs for an Additive Model $\alpha = 0.0001$ and $1 - \beta = 0.8$

	H ($\rho = 0$)				H ($\rho = 0.4$)			
P	0.05	0.1	0.2	0.3	0.05	0.1	0.2	0.3
0.1	2,874	692	199	106	1,533	374	106	61
	(4,578)	(1,093)	(294)	(147)	(2,800)	(668)	(174)	(91)
0.3	4,283	1,054	262	115	1,703	428	113	55
	(6,121)	(1,489)	(365)	(159)	(3,182)	(782)	(198)	(93)
0.5	5,095	1,284	313	132	1,751	444	117	56
	(7,123)	(1,788)	439)	(188)	(3,370)	(844)	(216)	(100)

Note: The sample size calculation is based on an equal mixture of ED and EC pairs and assumes that equal fractions of the four sub-types of EC and ED pairs, respectively. They may not apply to noticeably different mixture proportions.

required to achieve 80% power using the weighted tests are substantially lower than those needed by unweighted tests. This increases the feasibility of using ED and EC sib-pair designs.

It should be noted that the optimum weights for a weighted test statistic depend on the underlying genetic model and trait distribution. The sample sizes in Tables I and II are based on a bivariate normal distribution for the sib-pair trait values as in Risch and Zhang [1995, 1996].

Although the sample sizes presented here assumed that the recombination fraction θ is zero, using the arguments of Risch and Zhang [1996], the appropriate sample sizes for $\theta > 0$ can be obtained.

EC sib-pair procedures for QTL are similar to the affected sib pair (ASP) and affected-pedigree-member (APM) methods for binary traits [Whittemore and Halpern, 1994a,b]; Whittemore, 1996] that are based on the excess of allele-sharing between related individuals with similar phenotypes. The weights in the weighted test in this paper play the role of the score function in Whittemore and Halpern [1994b]. The optimum choice of weights will depend on the precise genetic model, which is often unknown. The simple weighting scheme used here, however, improved power for all three models considered. The smaller sample sizes required by the proposed weighted test should enhance the practical usefulness of ED and EC designs.

ACKNOWLEDGMENTS

This work was supported by National Cancer Institute CA64363 (to Z.L.) and an National Science Foundation grant (to J.G.) and was completed when J.G. was a visiting scientist at the Biostatistics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute. We thank Ms. Jinyu Yuan for excellent programming assistance and Professor D.C. Rao for many insightful comments.

REFERENCES

Blackwelder WC, Elston RC. 1985. A comparison of sib-pair linkage tests for disease susceptibility loci. Genet Epidemiol 2:85–97.

Carey G, Williamson J. 1991. Linkage analysis of quantitative traits: increased power by using selected samples. Am J Hum Genet 49:786–96.

Eaves L, Meyer J. 1994. Locating human quantitative trait loci: guidelines for the selection of sibling pairs for genotyping. Behav Genet 24:443–55.

Fulker DW, Cardon LR. 1994. A sib-pair approach to interval mapping of quantitative trait loci. Am J Hum Genet 54:1092–103.

Gu C, Todorov A, Rao DC. 1996. Combining extremely concordant sibpairs with extremely discordant sibpairs provides a cost effective way to linkage analysis of QTLs. Genet Epidemiol 13:513–33.

Haseman JK, Elston RC. 1972. The investigation of linkage between a quantitative trait and a marker locus. Behav Genet 2:3–19.

Kruglyak L, Lander ES. 1995. Complete multipoint sib-pair analysis of qualitative and quantitative trait. Am J Hum Genet 57:439–54.

Li Z, Zhang H. 2000. Mapping quantitative trait loci in humans using both extreme discordant and concordant sib pairs: a unified approach for meta-analysis. Commun Stat Theory Methods 29:1115–27.

Randles HR, Wolfe DA. 1979. Introduction to the theory of nonparametric statistics. New York: John Wiley & Sons.

Rao DC. 1998. CAT scans, PET scans, and genomic scans. Genet Epidemiol 15:1–18.

Risch N, Zhang H. 1995. Extreme discordant sib pairs for mapping quantitative trait loci in humans. Science 268:1584–9.

Risch N, Zhang H. 1996. Mapping quantitative trait loci with extreme discordant sib pairs: sample size considerations. Am J Hum Genet 58:836–43.

Sham PC, Zhao JH, Curtis D. 1997. Optimal weighting scheme for affected sib-pair analysis of sibship data. Ann Hum Genet 61:61–9.

Whittemore AS. 1996. Genome scanning for linkage: an overview. Am J Hum Genet 59:704–16.

Whittemore AS, Halpern J. 1994a. Probability of gene identity by descent: computation and applications. Biometrics 50:109–17.

Whittemore AS, Halper J. 1994b. A class of tests for linkage using affected pedigree members. Biometrics 50:118–27.

Zhang H, Risch N. 1996. Mapping quantitative trait loci in humans using extreme concordant sib pairs: selected sampling by parental phenotypes. Am J Hum Genet 59:951–7.

Zhao H, Zhang H, Rotter JI. 1997. Cost-effective sib-pair designs in the mapping of quantitative-trait loci. Am J Hum Genet 60:1211–21.